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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/229,173	01/13/1999	DEB K. CHATTERJEE	0942.2800008	7438

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EXAMINER	
HUTSON, RICHARD G	

ART UNIT	PAPER NUMBER
1652	21

DATE MAILED: 07/08/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/229,173	CHATTERJEE, DEB K.	
	Examin r	Art Unit	
	Richard G Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1,3,5-10,13,16,17,19,26,28,29,34-38 and 40-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *38 and 40-44* is/are allowed.

6)☐ Claim(s) *1,3,5-10,13,16,17,19,26,28,29 and 34-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Prosecution Application

The request filed on 2/19/2002 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/229,173 is acceptable and a CPA has been established. An action on the CPA follows.

Applicants cancellation of claims 4 and 39 without prejudice or disclaimer and amendment of claims 1, 5, 6, 36, 3738, 40 and 44, Paper No; 26, 5/1/2002, is acknowledged. Claims 1, 3, 5-10, 13, 16, 17, 19, 26, 28, 29, 34-38 and 40-44 are present for examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3, 5-10, 13, 16, 17, 19, 26, 28, 29 and 34-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 (3, 5-10, 13, 16, 17, 19, 26, 28, 29, 34-37 dependent from) is indefinite in that the metes and bounds of what applicants considers to be the "3'-5' exonuclease domain" and the "5'-3' exonuclease domain" of the claimed mutant *Thermotoga maritima* DNA polymerase mutants is unclear.

Claim 9 which is drawn to a mutant Tma DNA Polymerase as claimed in claim 1, wherein said mutant comprises both a $Phe^{730} \rightarrow Tyr^{730}$ substitution and a $Asp^{323} \rightarrow Ala^{323}$ substitution is included in this rejection and the 112 1st written description rejection below on the basis that it is not clear if the recited amino acid changes of claim 9 are the two **said** modifications of claim 1 or if they are amino acid modifications that are in addition to the two **said** modifications of the *Tma* DNA Polymerase **mutant** of claim 1. This indefiniteness results in part from claim 1 that recites "a Tma DNA Polymerase **mutant** which is modified at least two ways..." It is unclear if the "two modifications" results in the mutation of the Tma DNA Polymerase or if the Tma polymerase is mutated regardless of the two modifications. Are the two modifications of "a Tma DNA Polymerase" or of "a Tma DNA Polymerase mutant"? It is suggested that an amendment of claim 1 such as "A *Thermotoga maritima* (*Tma*) DNA polymerase [mutant] which is modified at least two ways..." in combination with an amendment of claim 9 such as "The mutant *Tma* DNA polymerase of claim 1, wherein the modifications are a $Phe^{730} \rightarrow Tyr^{730}$ substitution and a $Asp^{323} \rightarrow Ala^{323}$ substitution." would help applicants overcome this rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 5-10, 13, 16, 17, 19, 26, 28, 29 and 34-37 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The original rejection is stated in the previous office action, Paper No. 12, 11/21/2000.

Applicants have amended the claims such that the claimed Tma DNA Polymerase mutants are limited to mutations in the 3'-5' exonuclease domain or 5'-3' exonuclease domain or the O-helix of said polymerase. While applicants have narrowed the scope of the claimed Tma DNA polymerase mutants, the amended claims remain rejected.

The rejected claims are now directed to all possible *Thermotoga maritima* (*Tma*) DNA polymerase mutants which are modified at least two ways selected from the group consisting of (a) a mutation in the 3'-5' exonuclease domain of said polymerase to reduce or eliminate the 3' 5' exonuclease activity of the polymerase; (b) a mutation in the 5'-3' exonuclease domain of said polymerase to reduce or eliminate the 5'-3' exonuclease activity of the polymerase; and (c) a mutation in the O-helix of said polymerase to reduce or eliminate discriminatory behavior against a dideoxynucleotide and methods of using and kits comprising said DNA polymerase mutants and genes encoding said DNA polymerase mutants. The specification only provides a **Tne** DNA polymerase mutant consisting of a combination of the following mutations: those

mutants having reduced 3'-5' exonuclease activity consisting of Asp^{323} converted to Ala^{323}, those mutants having reduced discriminatory behavior against a dideoxynucleotides, consisting of Phe^{730} converted to Tyr^{730} and those mutants having reduced 5' 3' exonuclease activity consisting of the deletion of 219 amino terminal amino acids of Tne DNA Polymerase and Asp^{8} converted to Ala^{8} or Asp^{137} converted to Ala^{137} (Examples 11-13 and 16). There is no disclosure of any particular structure to function/activity relationship in the claimed genus. The specification also fails to describe additional representative species of these DNA Polymerases by any identifying structural characteristics or properties other than having reduced 3'-5' exonuclease activity of the polymerase, reduced 5'-3' exonuclease activity or reduced discriminatory behavior against dideoxynucleotides for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicants have previously argued that one of skill in the art could reasonably conclude that applicants had possession of the Tma DNA polymerase mutants encompassed by the rejected claims in the present application as filed. Applicants have submitted that the Examiner has underestimated both the teaching of the present application and the level of skill in the art and the examiner has done nothing more than argue lack of literal support in the application, failing to present evidence or reasons why one skilled in the art would not reasonably conclude that applicants were in

possession of the subject matter of the rejected claims. Applicants have submitted that the standard for fulfilling the written description requirement is whether the specification provides sufficient disclosure for one skilled in the art to readily envision a representative number of members of the claimed genus. Applicants have further submitted that at the time the invention was made, the sequence of many DNA polymerases had been compiled and aligned, showing that the DNA polymerases could be divided into several distinct families based on sequence homology. These distinct families of polymerases share many conserved sites throughout the protein and domains responsible for the various activities of the polymerases have been identified. Further still it has been shown that a number of mutations in the different polymerases within a family appear to be conserved throughout the family such that they result in the same functional modification of many of the polymerases of that family.

The claimed genus includes all possible *Thermotoga maritima* (*Tma*) DNA polymerase mutants which are modified at least two ways selected from the group consisting of (a) a mutation in the 3'-5' exonuclease domain of said polymerase to reduce or eliminate the 3'-5' exonuclease activity of the polymerase; (b) a mutation in the 5'-3' exonuclease domain of said polymerase to reduce or eliminate the 5'-3' exonuclease activity of the polymerase; and (c) a mutation in the O-helix of said polymerase to reduce or eliminate discriminatory behavior against a dideoxynucleotide, including any mutation of said domains including **amino acid substitutions, deletions and insertions of single as well as multiple amino acids**. As stated in the previous office action, there is no disclosure of any particular structure to function/activity

relationship in the claimed genus. While the specification provides the species, Asp^{323} $\rightarrow Ala^{323}$, (having reduced 3'-5' exonuclease activity), $Phe^{730} \rightarrow Tyr^{730}$ (having reduced discriminatory behavior against a dideoxynucleotides) and $Asp^{8} \rightarrow Ala^{8}$, $Asp^{137} \rightarrow Ala^{137}$ or the deletion of 219 amino terminal amino acids of Tne DNA Polymerase (having reduced 5'-3' exonuclease activity) encompassed by these claims, the specification clearly does not disclose a representative number of species of the claimed genus which includes an **infinite number of amino acid variants as well as additional chemical modifications** of any *Tma* DNA polymerases. Even considering the substantial knowledge of the skilled artisan, as detailed by applicants, one could only envision a small number of additional species within the scope of the claimed genus. However, in view of the enormous breadth of the claimed genus, even these could in no way be considered to be representative of the entire genus. There is no disclosure of any particular structure to function/activity relationship in the claimed genus. The disclosed species of mutant *Tma* DNA polymerases and others described in the art all have **minor** structural limitations such that the infinite number of species encompassed by this genus have not been adequately described by the few species disclosed in the specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Richard Hutson Ph.D.
Patent Examiner
Art Unit 1652
July 5, 2002